Opinion/Perspective
Sciences of Phytochemistry

A Beginner's Guide to Molecular Docking

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Abstract: In this opinion, the basics of molecular docking (MD) such as binding affinity, binding pose, and ligand interactions with common docking-related terminologies (Apo protein, positive control, native ligand, co-crystal inhibitors) are discussed. We have provided different figures to aid in the graphical interpretation of the discussed literature. Following this, a few advantages (simplicity, fast, applicability) and disadvantages of MD are highlighted. This opinion will benefit bachelor and master students (or anyone) that are interested in learning the technique of MD. We encourage the sensible use of the MD technique and strict analysis to avoid interpretation errors in the results. The binding affinity, binding pose, and ligand interactions should be collectively considered during the result analysis. For every study, we strongly recommend a strict validation of the docking protocols.

Introduction

Molecular docking (MD) is one of the computer-aided drug design (CADD) techniques (1). Under CADD, MD is considered a structure-based drug design (SBDD) technique (2). In the absence of a protein, SBDD such as MD cannot be carried out (3, 4). In this opinion paper, we will discuss some basics along with a few advantages and disadvantages of MD. This opinion will benefit bachelor and master students (or anyone) that are interested in learning the technique of MD.

The Basics

The binding affinity of a ligand towards the active binding site (orthosteric site) of a protein is studied with MD (see **Figure 1A**). The binding affinity of a ligand towards the non-active site (allosteric site) is also studied. Binding affinity is used synonymously with binding energy, but they have different meanings. The lower the binding energy, the higher the binding affinity, and vice versa. The unit 'kcal/mol' is usually associated with binding energy. Sometimes, researchers prefer to use the term 'docking score' instead of binding affinity/energy. Some software/web tool generates a unit-less value which is considered as docking score. Ultimately, a compound should have low binding energy, preferably lower than the native ligand (5, 6).

Native ligand (also referred to as standard/positive control/co-crystal inhibitor) is the compound that is complexed with the protein and they are usually present at the active binding site of the protein. However, not all molecules present at the active binding site are native ligands (see **Figure 1B**). A native ligand of a protein usually has supporting wet lab data (IC50, EC50, etc.) against the protein and this information can be found on the protein databank website. In MD, the native ligand is a positive control that serves as the benchmark with the efficacy of the test ligands will be judged. In the absence of a native ligand, it is important to search for a positive control from existing literature. The protein-free state (without any ligand) is called the Apo protein (7, 8).

The binding pose of a compound i.e. the spatial arrangement of a compound at the active binding site of a protein is studied with MD (**Figure 1C**). The active binding site contains all the important amino acids of the protein. One compound can have a different binding pose (spatial arrangement) at the active binding site. For instance, the PyRx virtual screening tool uses AutoDock Vina to generate 9 different binding poses for a single ligand and all the different binding poses have different binding affinities (**Figure 1D**) (9). A binding pose with the lowest binding energy (highest binding affinity) is usually considered the best pose.

The binding pose of a compound will determine what amino acids it interacts with (10, 11).

The molecular interactions between a protein and a ligand are studied with MD. In MD (**Figure 1E**), it is important to make sure that a potential lead compound has interacted with the amino acids that are present at the active binding site. Sometimes, the best binding pose with a very low binding energy can have fewer molecular interactions with the amino acids present at the active binding site. Sometimes, a compound may interact with multiple amino acids except for the amino acids present at the active binding site. Sometimes, a compound may also form different types of hydrophobic/electrostatic interactions except for conventional hydrogen bonds. Preferably, a compound must form more conventional hydrogen bonds with multiple amino acids at the active site. It may be noted that a higher number of conventional hydrogen bonds correlates to a lower possibility for the development of drug resistance (12, 13).

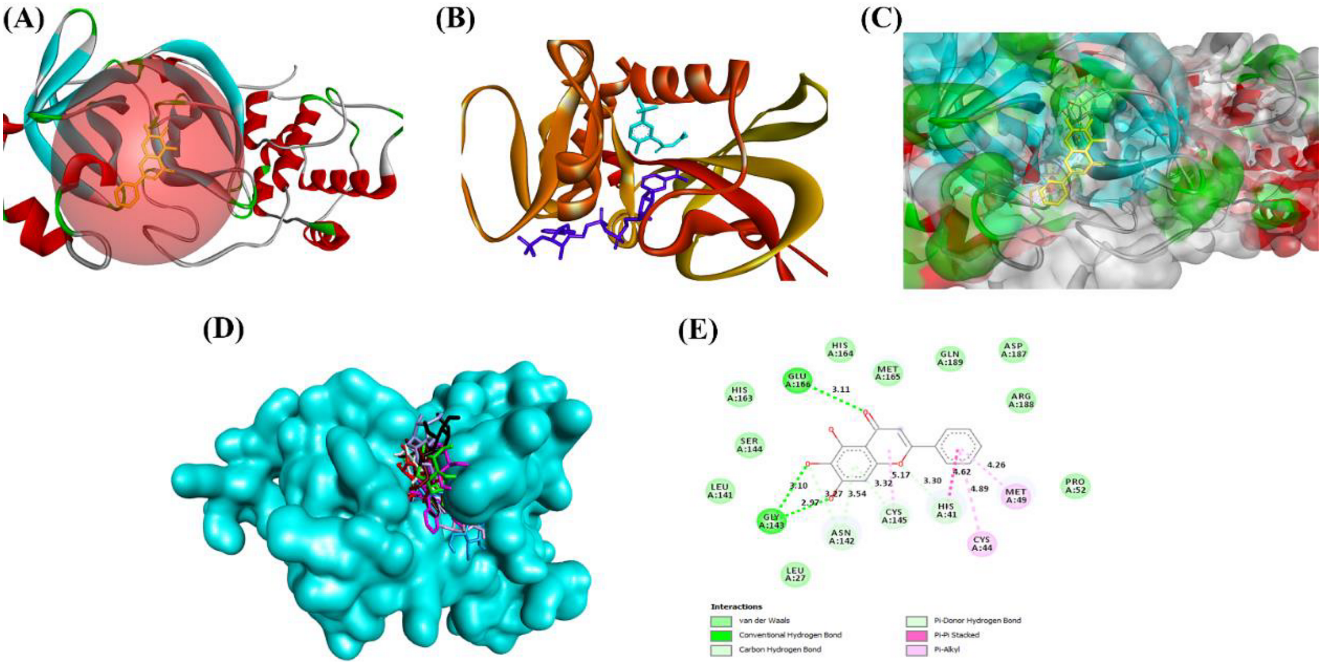

Figure 1. (A) Red sphere indicates the active binding site (allosteric site) of SARS-CoV-2 Mpro. The native ligand bound to the protein at the active binding site is presented in yellow color. (B) Two molecules are bound to the active binding site of PfDHFR-TS. The native ligand is depicted in light blue color while the other ligand in dark blue color is a peptide. (C) The binding pose of a ligand (yellow color) within the active binding pocket of SARS-CoV-2 Mpro. (D) The 9 different binding poses for a single compound at the active binding site of PfDHFR-TS. Each binding pose represented in different colors has a different binding affinity towards the protein. (E) Protein-ligand interactions between the native ligand and the amino acids at the active binding site of SARS-CoV-2 Mpro. There are 6 different types of interaction and the bond lengths are measured in Å units.

Advantages

1. In comparison to other in-silico techniques, MD is a simple technique as it can be easily and quickly executed.
2. A decent laptop (a simple workstation) is all it takes to perform MD. However, the workstation is also a factor in determining the speed of MD.
3. Using MD, we can study how the presence or absence of certain functional groups will impact the binding affinity of a ligand.
4. MD enables to rapidly evaluate the in-silico potency of virtually designed compounds against a target protein. This is useful to identify potential leads in a drug discovery program.
5. MD can be used to identify the key functional groups of a compound that will impact its binding affinity and interaction profiles. This information can be used to modify the structure of compounds to potentially improve the biological activity.

Disadvantages

1. The results of MD are preliminary as they are not fully reliable to make robust conclusions.
2. The results and conclusions of almost all studies carried out with MD include the term ‘potential’ as it is impossible to draw solid conclusions from the results of MD.
3. The results of MD are limited as it fails to represent some real biological phenomena.
4. For example, will the binding affinity remain at

the same value if the docking was to run for an extended time?
5. If we prolong the period of interaction, will the ligand remain stable (low binding energy) at the active site, or if it becomes unstable, what will be its fate?
6. Will the ligand maintain an adequate interaction with the active amino acids if the simulation time was extended?
7. Also, MD does not consider the temperature and pressure.
8. The docking protocols and docking results need to be validated by carrying out additional studies. Based on our personal publishing experience, MD studies require validation with either in-vitro studies or molecular dynamics simulations.

Author Perspective

We encourage the sensible use of the MD followed by strict analysis to avoid interpretation errors in the results. The binding affinity, binding pose, and ligand interactions should be collectively considered during the result analysis. For every study, we strongly recommend a strict validation of the docking protocols. For our studies, we routinely use the academic version of PyRx virtual screening tool (https://pyrx.sourceforge.io/). We also recommend the use of DockFlin (https://etflin.com/news/2), which is a product of ETFLIN. DockFlin is a multi-ligand and a multi-protein docking tool.

Declarations

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Conflict of Interest

The authors declare no conflicting interest.

Data Availability

Not applicable.

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Not applicable.

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